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(51) International Patent Classification 5 :
A61K 31/195, 31/22, 31/225
// C07C 323/59

A1

(11) International Publication Number: **WO 91/18594**

(43) International Publication Date: 12 December 1991 (12.12.91)

(21) International Application Number: PCT/SE91/00388

(22) International Filing Date: 3 June 1991 (03.06.91)

(30) Priority data:

9002067-8	8 June 1990 (08.06.90)	SE
9002275-7	28 June 1990 (28.06.90)	SE

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(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.

(54) Title: THE PHARMACOLOGICAL USE OF CERTAIN CYSTINE DERIVATIVES

(57) Abstract

A method for the treatment of diseases due to defects in the immune system using certain cystine derivatives and a pharmaceutical preparation comprising these derivatives.

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THE PHARMACOLOGICAL USE OF CERTAIN CYSTINE DERIVATIVES

Field of the Invention

The present invention relates to a new medical use of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N, N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester and N,N'-diisovalerylcystine dimethyl ester in racemic forms or in the form of optical D or L isomers.

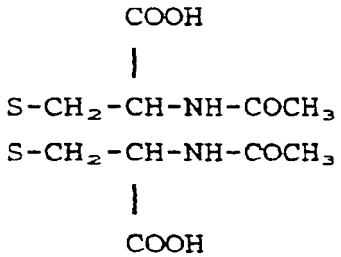
In particular the invention relates to the use of the abovementioned compounds for the preparation of medicaments with immunomodulating action, particularly immunostimulating action.

Background of the Invention

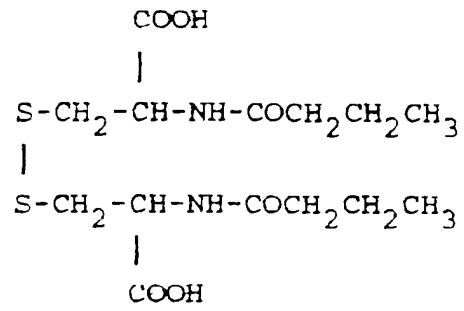
N-Acetyl-L-cysteine is a compound widely used for treating chronic obstructive airway diseases/chronic bronchitis (for further references see Multicentre Study Group. Long-term oral acetylcysteine in chronic bronchitis. A double-blind controlled study. Eur. J. Respir. Dis. 1980, 61 (suppl. 111), 93-108; Boman, G., Bäcker, U., Larsson, S., Melander, B., and Wåhlander, L. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis. Report of a trial organized by the Swedish Society for Pulmonary Disease. Eur. J. Respir. Dis. 1983, 64, 405-415; and British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airway obstruction. Thorax 1985, 40, 832-835). The mechanism of action of the compound is not disclosed; its effect has been attributed to mucolytic properties (see Multicentre Study Group.

Long-term oral acetylcysteine in chronic bronchitis. A double-blind controlled study. Eur. J. Respir. Dis. 1980, 61 (suppl. 111), 93-108; Boman, G., Bäcker, U., Larsson, S., Melander, B., and Wåhlander, L. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis. Report of a trial organized by the Swedish Society for Pulmonary Disease. Eur. J. Respir. Dis. 1983, 64, 405-415; and British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airway obstruction. Thorax 1985, 40, 832-835), antioxidant properties (see Aruoma, O.I., Halliwell, B., Hoey, B.M., and Butler, J. Free Radical Biol. Med. 1989, 6, 593-597), and also immunomodulating properties (see Bergstrand, H., Björnson, A., Eklund, A., Hernbrand, R., Eklund, A., Larsson, K., Linden M., and Nilsson, A. Stimuli-induced superoxide radical generation in vitro by human alveolar macrophages from smokers: Modulation by N-Acetylcysteine treatment in vivo. J. Free Radicals Biol. & Med. 2, 1986, 119-127).

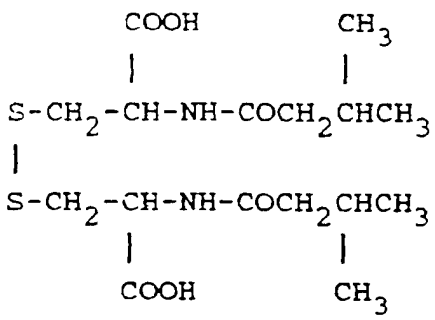
The present invention deals with the disulfide of N-acetylcysteine, that is N,N'-diacetylcystine (in the following referred to as DiNAC), i.e. the compound of the formula:



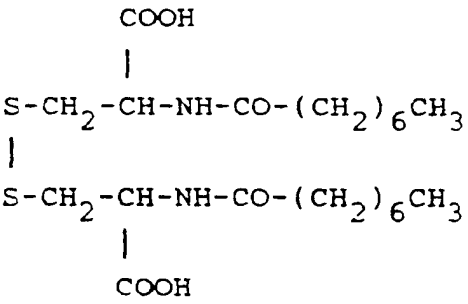
N,N' - dibutyrylcystine (in the following referred to as diBUT), i.e. the compound of the formula:



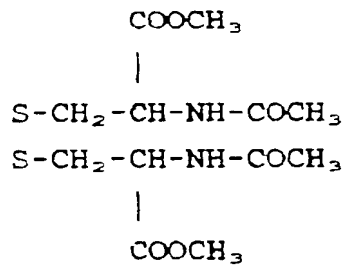
N,N'-diisovalerylcystine (in the following reffered to as diVAL), i.e. the compound of the formula



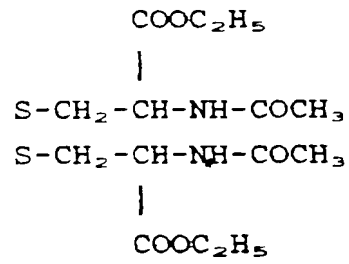
N,N'-dicaprylylcystine (in the following referred to as diCAP), i.e. the compound of the formula



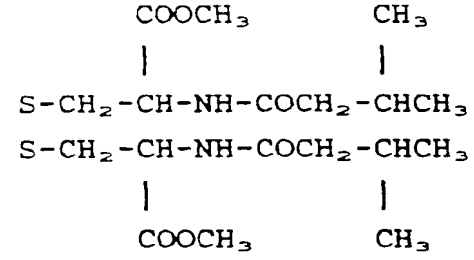
N,N'-diacetylcystine dimethyl ester (in the following referred to as diMeNAC), i.e. the compound of the formula:



N,N'-diacetylcystine diethyl ester (in the following referred to as diEtNAC), i.e. the compound of the formula:



and N,N'-diisovalerylcystine dimethyl ester (in the following referred to as diMeVAL), i.e. the compound of the formula:



The invention deals with the above mentioned compounds in racemic form as well as the isomeric D and L forms of the compounds. Of particular interest are the compounds having the L configuration, particularly interesting is N,N'-diacetyl-L-cystine.

The invention also deals with the compounds in the form of their physiologically acceptable salts such as the salts

of sodium, potassium, ammonium, calcium or magnesium. Also included are salts of the compounds diNAC, diBUT, diVAL and diCAP with pharmaceutically acceptable organic bases.

The above mentioned compounds have previously been described in the patent literature as well as in the scientific literature. DiNAC in the following publications: US 4827016; EP 300100; US 4724239; US 4708965; DE 2326444; Wilson, I.D., and Nicholson, J.K. Analysis of thiols and disulfides in Sulphur-containing drugs and related organic compounds. Chemistry, Biochemistry an Toxicology (ed L.A. Damani) Vol. 2A. Analytical, biochemical and toxicological aspects of sulphur xenobiochemistry. Ellis Horwood Series in Biochemical Pharmacology (Halstred Press: a division of John Wiley & Sons) Chichester 1989, p. 45; and Sjödin K., Nilsson E., Hallberg, A., and Tunek, A. Metabolism of N-Acetyl-L-cysteine. Some structural reguirements for the deacetylation and consequences for the oral biovailability. Biochem. Pharmacol. 1989, 38, 3981-3985). In US 4827016 the compound is claimed to be effective for topical treatment of dermal inflammations which are induced and propagated by leukotrienes.

The remaining compounds have also been described in the literature. (See for instance, for diMeNAC: Bowman, W.R. Richardson, G.D. Tetrahedron Lett. 1981, 22, 1551-1554; for diEtNAC: Damico, R.A. Boggs, R.W. US 3952115 (1976); for diVAL, diMeVAL: Martin, T.A. J. Med. Chem 1969, 12, 950-953), for diCAP: FR 8205 M, for diBUT: FR 2503151).

Nothing is reported or generally known concerning the pharmacological and/or therapeutic properties of these compounds with respect to immunological systems or inflammatory diseases of the lung such as chronic

bronchitis.

Disclosure of the Invention

It has unexpectedly been found that the hereinbefore mentioned compounds diNAC, diBUT, diVAL, diCAP, diMeNAC, diEtNAC and diMeVAL in an experimental animal model for assessing a T-cell reactivity in vivo, i.e. the delayed type hypersensitivity (DTH) reaction in the mouse ear, are highly potent and efficient immunostimulating agents, some being in the order of 100-1000 times more effective than the thiol NAC. Thus, in this model the compounds are highly effective immunostimulators with a potency and efficacy superior or equal to known immunostimulants such as diethyl dithiocarbamate (DTC) or hydroxyethyl disulfide (HEDS; see St Georgiev, V. New synthetic immunomodulating agents. Trends in Pharmacological Science 1988, 446-451).

Therefore, the compounds DiNAC, diBUT, diVAL, diCAP, diMeNAC, diEtNAC, diMeVAL and their D and L optical isomers may be used for treatment of diseases where a defect in the immune system and/or an ineffective host defence is at hand or can be suspected.

Examples of such diseases are chronic bronchitis and other inflammatory diseases of the airways such as asthma and rhinitis but also certain forms of autoimmune diseases like diabetes and rheumatoid arthritis and/or various malignant diseases. HIV infection or AIDS may be treated with the compounds. Also atherosclerotic disease may be treated with the compounds.

Effective amounts of the compounds diNAC, diBUT, diVAL, diCAP, diMeNAC, diEtNAC, diMeVAL and their D and L optical isomers for use in the treatment of the above mentioned

diseases are in the range 0.5-500 mg, preferably 5-50 mg, daily dose.

Synthesis of compounds

The compounds diNAC, diBUT, diVAL and diCAP may be prepared, for example, from L-cystine via acylation (see US 4827016; EP 300100; US 4724239; US 4708965; DE 2326444; Marshall, R., Winitz, M., Birnbaum, S.M. and Greenstein, J.P. J. Am. Chem. Soc. 1957, 79, 4538-4544; and Cecil, R. McPhee, J.B. Biochem. J. 1957, 66, 538-543) or through oxidative dimerization of the appropriate acylcysteines (see Snow, J.T., Finley, J.W. Friedman, M. Biochem. Biophys. Res. Commun. 1975, 64, 441-447).

The esters diMeNAC, diEtNAC and diMeVAL may be synthesized analogously, i.e. by acylation of the cystine methyl or ethyl esters as appropriate or by oxidative dimerisation of the respective N-acetyl cystine methyl or ethyl esters or N-isovalerylcysteine methyl ester. For examples of preparations, see Bonnett, R., Nicolaidow, P. J. Chem. Soc. Perkin Trans. I 1979, 1069-1077. Schaad, L.J., Werner, R.M., Dillon, L., Field, L., Tate, C.E. J. Med. Chem. 1975, 18, 344-351, and Martin, T.A. J. Med. Chem. 1969, 12, 950-953.

Effects of compounds in a model of delayed type hypersensitivity in the mouse

The property of the compounds diNAC, diBUT, diVAL, diCAP, diMeNAC, diEtNAC and diMeVAL to stimulate immune responses is illustrated by their efficacy in a model of the delayed type hypersensitivity (DTH) reaction in the mouse.

Both male and female Balb/c mice obtained from Bomholtsgaard (Denmark) and Charlie Rivers (England), were

used at the weight of 18-20 gram. 4-ethoxymethylene-2-phenyloxazolone (OXA) was purchased from BDH (England) and served as an antigen in this test.

The mice were sensitized, Day 0, by epicutaneous application of 150 µl absolute ethanol-acetone (3:1) solution containing 3% OXA on the shaved thorax and abdomen. Treatment with the L-form of diNAC, diMeNAC, diEtNAC, diMeVAL, or vehicle (phosphate buffer, pH 7.0) was initiated by oral feeding immediately after sensitization and continued once daily to Day 6. Seven days (Day 6) after the sensitization both ears of all mice were challenged on both sides by topical application of 20 µl 1% OXA dissolved in peanut oil. Ear thickness was measured prior to and 24 or 48 hours after challenge using an Oditest spring calliper. Challenges and measurements were performed under light pentobarbital anasthesia. The intensity of the DTH reactions was expressed according to the formula: $T_{t24/48}-T_{t0}$ µm units, where t0, t24 and t48 represent the ear thickness before and 24 or 48 hours after challenge, respectively, in an individual test (T). The results were expressed as the mean +/-S.E.M. The level of significance between means of the groups was obtained by Student's two-tailed t-test. Tables 1 and 2 show the results from 24 and 48 hours measurements, respectively, from a representative experiment with the L-form of diNAC. The results show that L-diNAC, after oral administration, caused a significant increase of the ear thickness in a concentration-response manner.

Table 1

Ear thickness 24 hours after challenge of animals treated with the indicated doses of L-diNAC or vehicle.

Conc. µmol/kg	N	Diff. $T_{t24}-T_{t0}$	S.E.M.	Sign.
Buffer	13	7.85	0.32	
NaCl	10	7.90	0.30	n.s.
0.03	10	13.75	0.47	***
0.30	10	15.70	0.48	***
3.0	10	18.30	1.02	***
30.0	15	20.67	0.67	***

***: $p < 0.001$

Table 2

Ear thickness 48 hours after challenge of animals treated with the indicated doses of L-diNAC or vehicle.

Conc. µmol/kg	N	Diff $T_{t48}-T_{t0}$	S.E.M.	Sign.
Buffer	14	9.64	0.35	
NaCl	10	9.85	0.54	n.s.
0.03	10	11.65	0.27	***
0.30	10	12.65	0.48	***
3.0	10	14.95	0.55	***
30.0	15	13.63	0.30	***

***: $p < 0.001$

Table 3 gives the correponding figures for ear thickness 24 and 48 hours after challenge of animals treated with diMeNAC and diEtNAC.

Table 3

Ear thickness 24 and 48 hours after challenge of animals treated with the L-forms of diMeNAC and diEtNAC.

	Conc µmol/kg	N	Diff $T_{t24}-T_{t0}$	S.E.M.	Sign.
24 h					
Buffer		10	8.70	0.34	-
diMeNAC	0.03	10	18.00	0.84	***
	3.0	10	12.55	0.88	**
diEtNAC	0.03	10	11.75	0.62	***
	3.0	10	13.05	0.59	***

(to continue...)

(...table 3)

	Conc µmol/kg	N	Diff $T_{t48}-T_{to}$	S.E.M.	Sign.
	48 h				
diMeNAC	0.03	10	12.85	0.67	**
	3.0	10	13.35	0.67	***
diEtNAC	0.03	10	13.15	0.53	***
	3.0	10	13.20	0.66	***

**: $p < 0.01$
***: $p < 0.001$

Pharmaceutical formulations

The described active substances can be included in different dosage forms e.g. tablets, coated tablets, gelatin capsules, solutions and aerosols.

For the preparation of tablets, coated tablets and gelatin capsules the active substances can be combined with pharmaceutically acceptable materials, e.g. lactose, starch, dicalcium phosphate, microcrystalline cellulose, polyvinylpyrrolidone, gelatin, cellulose derivatives, colloidal silicone dioxide, talc and stearic acid or its salts.

For the preparation of oral solutions suitable excipients are water, saccharose, glucose, sorbitol, fructose and xylitol.

The dosage forms can besides mentioned excipients contain preservatives, stabilizers, viscosity regulating agents, emulsifiers, sweetening agents, colouring agents, flavouring agents, tonicity regulating agents, buffers or antioxidants. They can also contain other therapeutically valuable substances.

Example 1

Tablet containing 10 mg of active substance per tablet:

Active substance	10 mg
Lactose	100 mg
Potato starch	50 mg
Polyvinylpyrrolidone	5 mg
Microcrystalline cellulose	15 mg
Magnesium stearate	1 mg

Example 2

Direct compression tablet containing 5 mg of active substance per tablet:

Active substance	5 mg
Lactose, anhydrous	150 mg
Microcrystalline cellulose	50 mg
Colloidal silicon dioxide	1 mg
Magnesium stearate	2 mg

If desired, the obtained tablets can be film coated with e.g. hydroxypropyl methylcellulose, hydroxypropyl cellulose or dimethylaminoethyl methacrylate methacrylic acid ester copolymer.

Example 3

Solution for injection containing active substance 1 mg/ml

Active substance	1.0 mg
Sodium chloride	8.8 mg
Water for injection	to 1 ml

Example 4

Oral solution containing active substance 1 mg/ml

Active substance	1.0	mg
Sorbitol	150	mg
Glycerin	100	mg
Disodium edetate	0.5	mg
Preservative	q.s.	
Flavour	q.s.	
Water, purified	to 1	ml

Example 5

Powder aerosol giving 1 mg per dose

The micronized active substance can be filled into a powder inhaler device e.g. Turbuhaler^{R} giving 1 mg/dose.

CLAIMS

1. The use of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with immunomodulating action.

2. The use of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, or a physiologically acceptable salt thereof for the preparation of medicaments with immunomodulating action.

3. The use according to claim 1 of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with effect against chronic bronchitis.

4. The use according to claim 2 of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, or a physiologically acceptable salt thereof

for the preparation of medicaments with effect against chronic bronchitis.

5. The use according to claim 1 of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with effect against asthma.

6. The use according to claim 2 of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, or a physiologically acceptable salt thereof for the preparation of medicaments with effect against asthma.

7. The use according to claim 1 of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with effect against rhinitis.

8. The use according to claim 2 of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-

diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, or a physiologically acceptable salt thereof for the preparation of medicaments with effect against rhinitis.

9. The use according to claim 1 of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with effect against diabetes.

10. The use according to claim 2 of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, or a physiologically acceptable salt thereof for the preparation of medicaments with effect against diabetes.

11. The use according to claim 1 of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with effect against rheumatoid

arthritis.

12. The use according to claim 2 of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, or a physiologically acceptable salt thereof for the preparation of medicaments with effect against rheumatoid arthritis.

13. The use according to claim 1 of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with effect against malignant diseases.

14. The use according to claim 2 of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, or a physiologically acceptable salt thereof for the preparation of medicaments with effect against malignant diseases.

15. The use according to claim 1 of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-

diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with effect against HIV infections/AIDS.

16. The use according to claim 2 of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, or a physiologically acceptable salt thereof for the preparation of medicaments with effect against HIV infections/AIDS.

17. The use according to claim 1 of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, D and L optical isomers thereof or a physiologically acceptable salt thereof for the preparation of medicaments with effect against atherosclerotic disease.

18. The use according to claim 2 of the L optical isomers of N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethyl ester, N,N'-diacetylcystine diethyl ester, N,N'-diisovalerylcystine dimethyl ester, or a physiologically acceptable salt thereof for the preparation of medicaments with effect against atherosclerotic disease.

19. The use according to claim 2 of N,N'-diacetyl-L-cystine.

20. A pharmaceutical preparation for use in the treatment of diseases where an immunomodulating substance is effective comprising as active ingredient a compound as defined in claim 1.

21. A pharmaceutical preparation according to claim 20 in dosage unit form.

22. A pharmaceutical preparation according to claims 20-21 comprising the active ingredient in association with a pharmaceutically acceptable carrier.

23. A pharmaceutical preparation according to claims 20-22 comprising as active ingredient N,N'-diacetyl-L-cystine.

24. A method for the treatment of diseases due to defects in the immune system, particulary chronic bronchitis, asthma, rhinitis, diabetes, rheumatoid arthritis, malignant diseases, HIV infection/AIDS and atherosclerotic disease, in mammals including man, characterized by the administration to a host in need of such treatment of an effective amount of racemic N,N'-diacetylcystine, N,N'-dibutyrylcystine, N,N'-diisovalerylcystine, N,N'-dicaprylylcystine, N,N'-diacetylcystine dimethylester, N,N'-diacetylcystine diethylester, N,N'-diisovalerylcystin dimethyl ester, D and L optical isomers thereof or a

physiologically acceptable salt thereof, optionally together with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00388

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 31/195, 31/22, 31/225//C 07 C 323/59

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K; C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP, A1, 0300100 (MORGAN LEE ROY) 25 January 1989, see claims 1, 12, 19-24, 25, 32, 39-42; p. 4, l. 14-19	1-19
X	--	20-23
A	US, A, 4827016 (L. R. MORGAN) 2 May 1989, see col. 5, l. 49-67; col. 7, l. 25-45; col. 10. l. 34-61; col. 11, l. 55 - col. 12, l. 9; col. 12, l. 22-57	1-19
X	--	20-23
A	US, A, 4724239 (L.R. MORGAN) 9 February 1988, see claims 1-4, 6-10, 12, 13, 15; col. 2, l. 34-40	1-19
X	--	20-23

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28th August 1991	1991 -09- 11
International Searching Authority	Signature of Authorized Officer
SWEDISH PATENT OFFICE	Gerd Wranne Gerd Wranne

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US, A, 4708965 (L.R. MORGAN) 24 November 1987, see claims 1-3, 5; col. 5, l. 50-67; col. 4, l. 19-28	1-19
X	--	20-23
A	Journal of Medicinal Chemistry, Vol. 18, No. 4, 1975 L.J. Schaad et al.: "Linear Regression Analysis of Inhibitory Potency of Organic Disulfides agains Histoplasma capsulatum", see p. 347, compound no. 72	1-19
X	--	20-23
A	Journal of Medicinal Chemistry, Vol. 12, September 1969 T.A. Martin: "N-Acyl- and N-Sulfonylcysteine Derivatives", see page 950 - page 953 see p. 952, Table I, compounds no. 19 and 20; p. 950. right col.,last paragr aph - p. 951, left col. first paragraph	1-19
X	--	20-23
A	FR, M, 8205 (J.V. MORELLE ET AL.) 26 October 1970, see claims 1, 2; p. 2; first paragraph, l. 28-31	1-19
X	--	20-23
A	FR, A1, 2503151 (J.V. MORELLE ET AL.) 8 October 1982, see p. 3; claims	1-19
X	--	20-23
P,X	International Journal of Pharmaceutics, Vol. 62, 1990 A.H. Kahns et al.: "Prodrugs as drug delivery systems. 107. Synthesis and chemical and enzymatic hydrolysis kinetics of various mono- and diester prodrugs of N-acetylcysteine", see page 193 - page 205 see the whole article	1-23
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X	Biochemical Pharmacology, Vol. 38, No. 22, 1989 K. Sjödin et al.: "Metabolism of N-acetyl-L-cysteine. Some structural requirements for the deacetylation and consequences for the oral bioavailability", see page 3981 - page 3985 see the whole article	1-23
	--	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	US, A, 3952115 (R.A. DAMICO ET AL.) 20 April 1976, see claims 1, 5, 6, 8-10; col. 5, l. 17-30; col. 9, l. 63 - col. 10, l. 5; col. 10, l. 68 - col. 11, l. 1 --	1-23
A	Tetrahedron Letters, Vol. 22, No. 16, 1981 W.R. Bowman et al.: "Reactions of thiolate anions with 2-substituted-2-nitropropanes", see page 1551 - page 1554 see p. 1552, the Table, last compound --	1-23
A	DE, A, 2326444 (THE PROCTER & GAMBLE CO.) 6 December 1973, see p. 7, 3:rd paragraph; p. 8; p. 20, 2:nd paragraph; p. 21, last paragraph; p. 22, last paragraph - p. 23, first paragraph --	1-23
A	Patent Abstracts of Japan, Vol 12, No 47, C475, abstract of JP 62-195356, publ 1987-08-28 SEIWA KASEI K.K. --	1-23
A	J. Org. Chem., Vol. 54, 1989 D.S. Kemp et al.: "Templates for Intramolecular O,N-Acyl Transfer via Cyclic Intermediates Derived from Mercury Derivatives of L-Cysteine: Progress toward a Mercury-Based Thiol Capture Strategy", see page 3853 - page 3858 see p. 3855, right col. 2:nd paragraph --	1-23

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim number(s) 24, because ~~they~~ it relate(s) to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods. /PCT Rule 39.1 (iv)/.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00388

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 91-06-27
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A1- 0300100	89-01-25	US-A-	4708965	87-11-24
		US-A-	4827016	89-05-02
US-A- 4827016	89-05-02	US-A-	4724239	88-02-09
		EP-A-	0300100	89-01-25
		US-A-	4708965	87-11-24
US-A- 4724239	88-02-09	US-A-	4827016	89-05-02
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		AU-B-	506795	80-01-24
		AU-D-	1235476	77-09-29
		BE-A-	840351	76-10-04
		CA-A-	1064316	79-10-16
		CH-A-	623206	81-05-29
		DE-A-B-C	2613786	76-10-14
		FR-A-B-	2305938	76-10-29
		GB-A-	1533780	78-11-29
		JP-A-	51142551	76-12-08
		NL-A-	7603445	76-10-05
		SE-B-C-	423301	82-05-03
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		AU-B-	472310	76-05-20
		AU-D-	5593173	74-11-21
		BE-A-	800030	73-11-26
		CA-A-	1004905	77-02-08
		CH-A-	583003	76-12-31
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		FR-A-B-	2185360	74-01-04
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The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP-B- 50037731	75-12-04
		NL-A- 7307293	73-11-27
		SE-B-C- 388113	76-09-27
		US-A- 3878305	75-04-15